Antimicrobial-Drug Use and Methicillin-Resistant *Staphylococcus aureus*

To the Editor: We read with great interest the debate on the contribution of antimicrobial selection pressure to changes in resistance in *Salmonella enterica* serovar Typhimurium and the comparison made with methicillin-resistant *Staphylococcus aureus* (MRSA) (1).

We strongly agree with Davis et al. that infection control practices must play a central role in successful MRSA control programs. However, we disagree that the antimicrobial-drug use practices that contribute to the control of MRSA have not been scientifically defined. In a recent review, we identified more than 20 studies on consistent associations, dose-effect relationships, and concomitant variations, all supporting a causal relationship between antimicrobial-drug use and MRSA (2).

Since our review, seven other studies have reported on the contribution of antimicrobial-drug use to MRSA colonization and infection in patients, or to high MRSA rates in health-care settings (3-9). One study reports a decrease in the rate of new MRSA cases after major reduction in antimicrobial-drug use (5). Although a lower number of discharges and a shorter hospital stay recorded during the 2-year postintervention period have been proposed as other explanations (10), the sharp decrease in new MRSA cases after the new antibiotic formulary was implemented (a delay of only a few months) supports the hypothesis that reduced antimicrobial pressure contributed to the decline. Additionally, at the recent 4th Decennial International Conference on Nosocomial and Healthcare-Associated Infections, at least five reports addressed either (a) antimicrobial-drug use and increased MRSA incidence or (b) antimicrobial-drug use as an independent risk factor for MRSA acquisition or for persistent MRSA colonization after mupirocin treatment (11).

When antimicrobial classes are taken into account separately, cephalosporins and fluoroquinolones are often identified as risk factors for MRSA (2-5,8,11). The mechanisms that would explain the participation of these two classes are not fully understood. However, fluoroquinolones directly enhance the expression of high-level oxacillin-resistant *S. aureus* in vitro (11, p.202). Another recent study shows that sub-MIC levels of ciprofloxacin increase adhesion of quinolone-resistant MRSA (12), which could explain persistent MRSA colonization and failure of mupirocin treatment in patients who received a fluoroquinolone (11, p.197). MRSA outbreaks in surgical patients have been controlled by isolating patients and abandoning third-generation cephalosporins for surgical prophylaxis (3). As stated by Davis et al., dissemination of epidemic clones does not necessarily require antimicrobial selection pressure; however, the above studies suggest participation of antimicrobial drugs in MRSA colonization and outbreaks.

Finally, when citing Dutch infection control measures as an example of successful control of MRSA, Davis et al. omit the fact that, among European countries, the Netherlands has the lowest antimicrobial-drug use in primary health

care (13) and one of the lowest in hospitals (14). Similarly, Nordic European countries report both very low MRSA prevalence and antimicrobial-drug use (13,15). In Denmark, the prevalence of MRSA peaked at approximately 18% among all *S. aureus* isolates (and approximately 30% among blood isolates only) at the end of the 1960s, then regularly decreased during the 10 following years. This decrease has been attributed to various interventions, including increasing awareness of hospital hygiene and an intensive campaign to teach physicians the principles of prudent antimicrobial-drug use. Indeed, the decade witnessed a decrease in the use of streptomycin and tetracycline to which these MRSA strains were resistant. However, determining the relative contribution of these interventions to the disappearance of MRSA strains from Denmark has not been possible since all were implemented at approximately the same time. Since the beginning of the 1980s, the percentage of MRSA has remained extremely low, and below 1% among blood *S. aureus* isolates. Except for a very small number of localized hospital outbreaks, Danish MRSA isolates now represent imported cases from countries with high prevalence. To preserve this low level, patients admitted from foreign hospitals are isolated and screened for MRSA carriage. Health-care workers who have been working in foreign hospitals are also screened before working in Danish hospitals. At the same time, both the overall level of antimicrobial-drug use and the fraction represented by broad-spectrum antimicrobial drugs, such as cephalosporins or fluoroquinolones, remain very low in Danish primary health care and hospitals, according to the 1999 report by the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (available from: URL: http://www.svs.dk/dk/Organisation/z/forsider/Danmap%20forsider.htm).

Additional research is certainly needed to fully understand the relationship between antimicrobial use and MRSA. However, the evidence supports implementation of programs to control or improve prescriptions when infection control alone does not control MRSA or the organization and resources for a "search-and-destroy" MRSA control strategy are not available.

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